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LOCAL INTERFERON THERAPY OF OSTEOLYTIC BONE METASTASES

[Lokale Interferontherapie metastatisch bedingter Osteolysen]

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Local Interferon Therapy of Osteolytic Bone Metastases

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[Abstract already translated]

Introduction

The treatment of bone metastases has gained great importance in palliative tumor therapy. As a consequence of the improved and more successful regimes in the primary therapy of malignant diseases, the frequency of the occurrence of metastases has increased during the course of the illness. The skeletal system is frequently affected. A surgical intervention appears merely indicated only in individual cases (acute cross section symptomatic with bone marrow compression, pathologic fractures, acute static risks). In the majority of the cases are indicated conservative measures, with which has been obtained considerable progress in the last few years.

The following therapy modalities are considered secure today:

1. The radiotherapy as locally highly effective method achieves excellent palliative effects (1) in particular in bone metastases.

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[1] Numbers in the margin indicate pagination in the foreign text.

2. The cytostatic chemotherapy with systemic effect on proliferating cells is indicated for extensive bone filializing of cytostatic-sensitive tumors.
3. The hormone therapy effects a proliferation inhibition as further systemic measure in hormone-sensitive tumors (for example, breast cancer, prostate cancer).

An improvement of the treatment results that goes beyond this can be achieved by an optimized timing with respect to the combination of the mentioned therapy modalities. The simultaneous application of radiation and cytostatic chemotherapy appears advantageous, whereas the simultaneous application of hormonal and radiotherapeutic and chemotherapeutic measures should be evaluated rather conservatively. This results also due to basic, methodic considerations as well as also from the results of the corresponding research and therapy protocols as already explained earlier [2-13]. According to the studies available until now, remission rates of 90% can be obtained in certain types of tumors also in the metastasized state by means of an optimized chronological coordination of radiation and chemotherapy [7-10, 12].

In the development of new antineoplastically active agents is promoted in the palliative treatment of tumor patients, aside

from a high effectiveness, also to a special extent a lower toxicity and therewith a better tolerance. These criteria appear to be fulfilled according to the previous experiences, among other things, in the interferon therapy of some malignant tumors.

Interferons are proteins or glycoproteins with a molecular weight of 20,000 Dalton.

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Table 1: Nomenclature of Human Interferon (IFN)

Old Terminology	New Terminology	
	Natural Interferons	Recombinant Interferons
Leucocytes	n-IFN-α-18 i.m.s.c.	r-IFN-α i.m.s.c.
Fibroblasts-IFN	n-IFN-β-(Fiblaferon®) i.v. local	r-IFN-β i.v. local
Immune-IFN	n-IFN-γ i.m.s.c.	n-IFN-α i.v.i.m.s.c.

In accordance with their different immunologic behavior can be differentiated 3 interferon classes: alpha, beta, and gamma interferon.

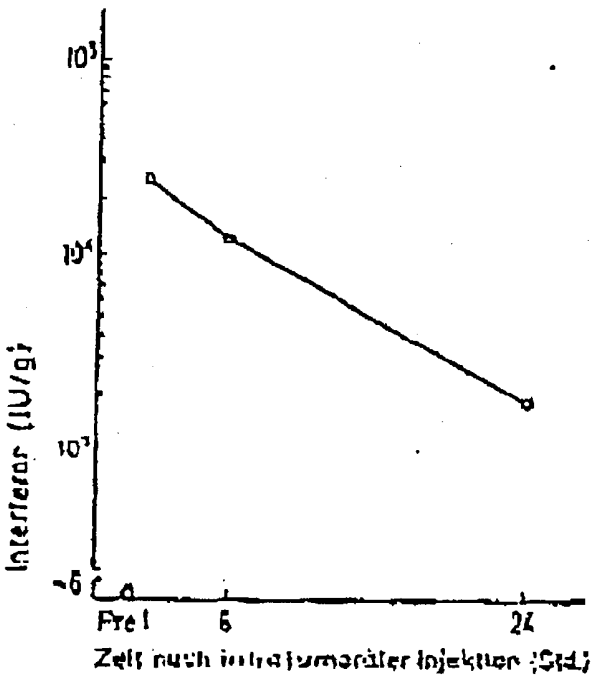
There are additional differences with respect to the production process. The so-called natural interferons are obtained by stimulating human leucocytes or fibroblasts, whereas the recombinant interferons are produced above all by using E. coli treated with gene technology.

Beta and gamma interferons are monosubstances; there are, according to our current knowledge, about 16 subtypes of natural alpha interferons. All the interferons have in common that they have antiviral, immunomodulating, and antiproliferating properties by interacting with a specific cell receptor [14]. These properties appear to be identical for alpha and beta interferon, while gamma interferon unfolds its effect over a specific receptor.

Due to their in part very similar properties, alpha and beta interferons are grouped together as type-I interferons; gamma interferons are also called type-II interferons (Table 1). Despite the similar pharmacodynamic properties, the alpha and beta interferons show a different pharmacokinetic behavior. In cases of local application, beta interferon is retained in contrast with the alpha interferons over several hours at the injection location and diffuses only slowly into the blood plasma [15-17].

In Fig. 1 is shown the concentration curve after intratumoral injection of 10^3 IU IFN-beta in 1 ml isotonic NaCl solution at the injection location. In the corresponding tissue samples is not detected a considerable reduction of the level;

Fig. 1



Legend to Fig. 1: Zeit nach intratumoraler Injektion (Std.) = Time after Intratumoral Injection (Hours).

Fig. 1: Course of interferon level at the place of injection after application of 10^3 IU IFN-beta

the interferon concentration in the blood was underneath the detection threshold during the entire observation time. The intravenous administration of the same dose of beta inferon leads to an increase of the concentration to a maximum of 10 IU/ml with a serum half-life of approx. 1 hour. From the intradermal application also of the same dose results after 6 hours a tissue concentration of more than 10^3 IU IFN-beta interferon/g of tissue. By means of a local injection of beta interferon can be obtained in this way over 1000 times higher intratumoral concentrations than with the i.v. administration. According to the mentioned findings and taking into consideration the numerous existing previous clinical experiences [among others 15-21], it appears to us that the carrying out of a study about a local interferon therapy for the treatment of osteolytic bone metastases is justified so as to be informed about its results afterward.

Material and Methods

Patients

A total of 40 patients, 10 male and 30 female, were treated within the scope of this study within the period from 1/1984 to 7/1985. The average age was 57 years (range: 28 to 80 years of age). As primary tumor was found breast cancer in 28 female patients (70%), prostate cancer in 5 patients (12.5%), as well

as a bronchial carcinoma in 3 patients (7.5%); 2 patients (5%) had as primary illness a kidney cell carcinoma, another 2 patients had other malignant tumors (Table 2). In 87% of the cases, a palliative radiotherapy as well as 58% of a cytostatic chemotherapy interferon treatment would have preceded the interferon treatment. All the patients had a surgical pretreatment. The metastatic osteolyses are predominantly diagnosed in the ribs (37.5%) as well as in the spinal column (32.5%). 20% of the osteolyses were also discovered in the pelvic area. The diagnosis preparation took place in all the cases based on a skeletal scintigraphy and X-rays. The effect of the therapy was verified in all patients with X-rays, and in the majority of the cases also in addition with a skeletal scintigraphy.

Table 2: Distribution of the Treated Patients according to the Tumor Sites

Localization of the Tumor Site	Number of Patients	%
Breast	28	70.0
Prostate	5	12.5
Bronchia	3	7.5
Kidneys	2	5.0
Other	2	5.0

Total	40	100.0

The beta or gamma interferon was injected directly into the osteolyses. The application took place under radioscopical control. 25 patients were treated with gamma interferon of the Rentschler Company, D-7958 Laupheim. The individual dose amounted from 2.5 x 10^3 to 5 x 10^3 IE 3 times a week. Each patient received an average of 25 injections. 15 patients were administered beta interferon of the Rentschler Company, D-7958 Laupheim. The application took place also 3 x a week in one individual dose of 5 x 10^3 IE beta interferon. An average of 13

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treatments were carried out. During the interferon therapy were not carried out other therapy measures (radiation, hormones, cytostatic chemotherapy).

Results

Of the 40 patients, 39 were statically evaluated after the study was concluded. The therapy was very well tolerated in all cases, there were no local or systemic side effects. The treatment results were evaluated as follows based on the UICC criteria:

- Full remission: complete recalcification shown in the X-ray
- Partial remission: more than 50% recalcification

- "No change": less than 50% recalcification or local progression of no more than 25%
- Progression: increase of the osteolysis by more than 25%
- NC + as additional criterion in the case of a subjective improvement (freedom of pain) with simultaneously unchanged findings in the X-rays.

According to this, a full remission occurred in one patient (2.6%), in 15 patients (38.4%) was determined a partial remission. The criteria of the category "NC+" were fulfilled by 16 patients (41.0%). In 4 cases (10.3%) could not be detected a significant improvement, either subjectively or objectively. 3 patients (7.7%) showed signs of progression. From this results a response ratio of 81.7% (Table 3). An exemplary case is shown in Fig. 2.

Table 3: Overall Response Rates

Responses	Number of Patients	%
CR	1	2.6
PR	15	38.4
NC+	16	41.0
NC	4	10.3
PD	3	7.7
Total	39	100.0

Table 4: Response Rates of Beta Interferon

Responses	Number of Patients	%
CR	1	6.7
PR	7	46.6
NC+	6	40.0
NC	0	0.0
PD	1	6.7
Total	15	100.0

Table 5: Response Rates of Gamma Interferon

Responses	Number of Patients	%
CR	0	0.0
PR	8	33.3
NC+	10	41.7
NC	4	16.7
PD	2	8.3
Total	24	100.0

The success of the interferon therapy can be seen clearly in the comparison of the condition before (a) and after (b) the therapy. The mentioned results refer to the patients treated with beta interferon as well as to those treated with gamma

interferon. The results of the two groups are shown separately in Tables 4 and 5.

In the cases treated with beta interferon was achieved a full remission in one patient (6.7%). 7 patients (46.6%) showed a partial remission, and in 6 cases (40.0%) was achieved a freedom from pain with radiologically unchanged condition (NC+). Merely one patient (6.7%) showed signs of progression. No patients of this group were classified in the category "No change." The total response ratio for beta interferon is therewith at 93.3%.

The application of gamma interferon led in 8 cases (33.3%) to a partial remission; the criteria of the category "NC+" were fulfilled by 10 patients (41.7%). In 4 patients (16.7%) was shown neither an objective nor a subjective condition change. In two cases (8.3%) was determined a progression. Overall resulted with this group a response rate of 75%.

Separately evaluated were also all the patients with breast cancer as primary tumor (Table 6). In one case (3.7%) was achieved a full remission, in 13 patients (48.2%) was observed a partial remission. A freedom of pain without objective condition change (NC+) could be achieved in 8 cases (29.6%). 4 patients (14.8%)

did not show an improvement neither subjectively nor objective; in one case (3.7%) were found signs of progression. The total response ratio amounted to 81.5%.

With respect to the remission duration (Table 7) is also recognized a clear dependency from the degree of remission within the scope of this study; the longest progression-free interval was shown to be 14 months in those patients in which a full remission had been obtained. In patients with partial remissions, the average partial remission lasted for 8.8 months.

Table 7: Duration of the Remissions (Overall).

Responses	Months
CR	14.0
PR	8.8
NC+	7.9
NC	6.0

In the category NC+ could be determined a new progression after an average of 7.9 months. The shortest remission times in on average 6.0 months could be observed in the cases which had shown neither a significant condition change nor a subjective improvement (No change).

Fig. 2

Abbildung 2: Beispiel einer erfolgreichen Interferon-Therapie bei einem Patienten mit Mammakarzinom: a) vor, b) nach Interferon.
Example of a successfully treated patient with breast cancer a) before treatment, b) after treatment.

Fig. 2: Example of a successfully treated patient with breast cancer (a) before treatment, (b) after treatment.

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Table 6: Response Rates in Breast Cancer

Responses	Number of Patients	%
CR	1	3.7
PR	13	48.2
NC+	8	29.6
NC	4	14.8
PD	1	3.7
Total	27	100.0

Discussion

Initially was emphasized for the substances used for palliative tumor therapy in particular the requirement of a lower toxicity but with a still high effectiveness. According to the shown results of this study, it appears that the two criteria for the local interferon therapy of osteolytic bone metastases are fulfilled. No side effects of systemic or local type were detected in any of the cases. The response rates were with 75-93% relatively high, with remission durations of up to 14 months (x - 8.5 months). Beta interferon is possibly superior in its effectiveness with respect to gamma interferon in the mentioned application mode; a sufficiently founded statement cannot be made about this taking into consideration the low case number. Based on the conditions recorded within the scope of this research, it could be justified to verify these results with a greater group of patients in a randomized phase-III study, whereas even before starting should be clarified the matters of the optimized dose as well as the total duration of the treatment to be sought. It would also be of interest to find out if the use of beta interferon does actually offer the implied advantages with respect to gamma interferon in the indication to be discussed. Insofar as can be evaluated from the results obtained so far, it appears that this is a

therapeutic formulation for the local interferon treatment of osteolytic bone metastases that merits further testing.

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